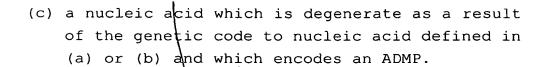
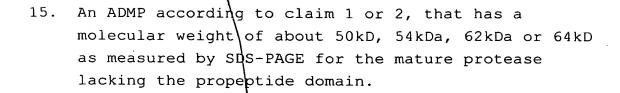
What is claimed:

- 1. An isolated ADMP, cleaving the Glu^{373} -Ala 374 peptide bond of an aggrecan core protein.
- 2. An isolated ADMP, wherein said ADMP has the property of cleaving the Glu³⁷³-Ala³⁷⁴ peptide bond of the aggrecan core protein and wherein said ADMP consists of the following domains from the N-terminus to the C-terminus: 1) a propeptide domain containing a furin cleavage site, followed by 2) a metalloprotease domain, followed by 3) a disintegrin-like domain, and 4) a thrombospondin homologous domain
- A non-glycosylated ADMP according to claim 1 or 2 in isolated form.
- 4. An ADMP according to claim 1 or 2, having a molecular weight between about 35kD and about 120kD, as measured by SDS-PAGE.
- 5. An ADMP according to claim 1 or 2, having a molecular weight between about 45kD and about 100kD, as measured by SDS-PAGE.
- 6. An ADMP according to claim 1 or 2 having a molecular weight between about 50kD and about 98kD, as measured by SDS-PAGE.
- 7. An isolated nucleic acid selected from the group comprising:
 - (a) a coding region of a gene encoding a native mammalian ADMP of claim 1;
 - (b) a nucleic acid that is at least 80% identical to the nucleic acid of (a) and that encodes an ADMP;

or



- 8. An isolated nucleid acid according to claim 7, wherein the ADMP is a human ADMP.
- 9. An isolated nucleic acid of claim 7 or 8 which encodes an active ADMP variant or ADMP derivative.
- 10. An ADMP according to claim 1 or 2, that has a molecular weight of about 98kD for the zymogen as measured by the SDS-PAGE.
- 11. An ADMP according to claim 1 or 2, that has a molecular weight of about 67kD as measured by SDS-PAGE for the mature form of the protease lacking the propeptide domain.
- 12. An isolated nucleic acid selected from the group comprising:
 - (a) a coding region of a gene encoding native mammalian ADMP of claim 10;
 - (b) a cDNA comprising nucleotides 406-2919 of SEQ ID NO:1;
 - (c) a nucleic acid that is at least 80% identical to the nucleic acid of (a) or (b) and that encodes an ADMP; or
 - (d) a nucleic acid which is degenerate as a result of the genetic code to nucleic acid defined in (a), (b) or (c) and which encodes an ADMP.
- 13. An isolated nucleic acid according to claim 12, wherein the ADMP is a human ADMP.
- 14. An ADMP according to claim 1 or 2 that has a molecular weight of about 93kD for the zymogen as measured by SDS-PAGE.



- 16. A composition comprising an ADMP as in any of claims 1 or 2.
- 17. An isolated nucleid acid selected from the group comprising:
 - (a) a coding region of a gene encoding native mammalian ADMF having a molecular weight of about 93kD as measured by SDS-PAGE;
 - (b) a cDNA comprising nucleotides 121-2910 of SEQ ID NO:14;
 - (c) a nucleic acid that is at least 80% identical to the nucleic acid of (a) or (b) and that encodes an ADMP and
 - (d) a nucleic acid which is degenerate as a result of the genetic code to nucleic acid defined in(a),(b) or (c) and which encodes an ADMP.
- 18. An isolated nucleic acid according to claim 17, wherein the ADMP is a human ADMP.
- 19. An antibody that binds to an ADMP according to claim 1.
- 20. An antibody according to claim 19, wherein the antibody is a monoclonal antibody.
- 21. An expression vector that directs the expression of a nucleic acid sequence as in any of claims 7,8,12,13,17 or 18.
- 22. A host cell transfected or transformed with an

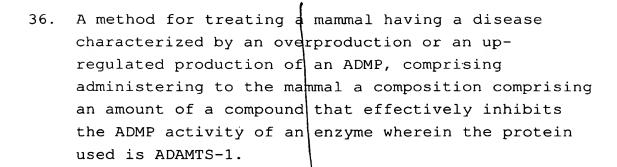


expression vector that directs the expression of a nucleic acid sequence as in any of claims 7,8,12,13,17 or 18.

- 23. A method for producing an ADMP, comprising:
 - (a) culturing a host cell under conditions promoting expression; and
 - b) recovering the ADMP from the culture medium.
- 24. ADMPs produced according to claim 23.
- 25. ADMP-1 comprising the sequence of amino acids 1-837 of SEQ.ID NO:2.
- 26. ADMP-2 comprising the sequence of amino acids 1-930 of SEQ.ID NO:15.
- 27. A method of identifying cell lines, cells or tissues that produce ADMPs using a nucleic acid probe which hybridizes with a native ADMP nucleic acid sequence according to any of claims 7,8,12,13,17 or 18 to detect ADMP message in biological samples.
- 28. The use of an ADMP according to any of claims 1 or 2 or 25 or 26 for three-dimensional structural analysis and computer-aided drug design of ADMP inhibitors.
- 29. A method of inhibiting the cleavage of aggrecan in a mammal comprising administering to such mammal an effective amount of a compound that inhibits the proteolytic activity of an ADMP as in any of claims 1 or 2 or 25 or 26.
- 30. A method for treating a mammal having a disease characterized by an overproduction or an up-regulated production of an ADMP comprising administering to the mammal a pharmaceutical

composition comprising an amount of a compound that effectively inhibits the proteolytic activity of an ADMP as in any of claims 1 or 2 or 25 or 26.

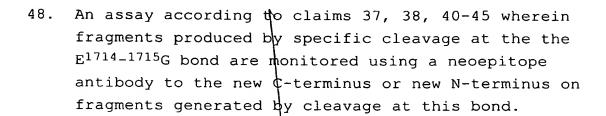
- 31. A method of inhibiting the cleavage of aggrecan in a mammal comprising administering to such mammal an effective amount of a compound that inhibits the isolated ADMP comprising the sequence of amino acids 1-837 of SEQ ID NO:2.
- 32. A method for treating a mammal having a disease characterized by an overproduction or an upregulated production of an ADMP, comprising administering to the mammal a composition comprising an amount of a compound that effectively inhibits the ADMP activity of an enzyme comprising the sequence of amino acids 1-837 of SEQ ID NO:2.
- 33. A method of inhibiting the cleavage of aggrecan in a mammal comprising administering to such mammal an effective amount of a compound that inhibits the isolated ADMP comprising the sequence of amino acids 1-930 of SEQ ID NO:15.
- 34. A method of inhibiting the cleavage of aggrecan in a mammal comprising administering to such mammal an effective amount of a compound that inhibits the ADMP activity of an enzyme wherein the protein used is ADAMTS-1.
- 35. A method for treating a mammal having a disease characterized by an overproduction or an upregulated production of an ADMP, comprising administering to the mammal a composition comprising an amount of a compound that effectively inhibits the ADMP activity of an enzyme comprising the sequence of amino acids 1-930 of SEQ ID NO:15.



- 37. An assay for ADMP activity and inhibitors of ADMPs, which comprises:
 - (a) generating soluble ADMPs, by stimulation of human or animal tissue or cells;
 - (b) detecting ADMP enzymatic activity by using the soluble ADMPs generated in (a) or any ADMP-containing sample, incubating with an aggrecan substrate in absence or presence of an inhibitor, and monitoring production of aggrecan fragments produced by specific cleavage at an ADMP-susceptible site using a necepitope antibody to the new N-terminus or C-terminus generated by ADMP-mediated cleavage;
 - (c) evaluating inhibition of ADMP activity by comparing the amount of product produced in the presence versus absence of compound.
- 38. An assay according to claim 37 wherein the tissue or cell source of ADMPs is cartilage or chondrocytes.
- 39. An assay according to claim 37 or 38 wherein the aggrecan substrate is aggrecan isolated from human or animal tissue.
- 40. An assay according to claim 37 wherein the

aggrecan substrate is a recombinant aggrecan molecule or recombinant portion of the aggrecan molecule containing an aggrecanase-sensitive cleavage site.

- 41. An assay according to claim 40 wherein the recombinant portion of the aggrecan molecule contains the $E^{373-374}A$ bond.
- 42. An assay according to claim 40 wherein the recombinant aggreean fragment contains the E^{1545} -1546G bond.
- 43. An assay according to claim 40 wherein the portion of the aggrecan molecule contains the E^{1714} -1715G bond.
- 44. An assay according to claim 40 wherein the recombinant portion of the aggrecan molecule contains the $\rm E^{1819-1820}A$ bond.
- 45. An assay according to claim 40 wherein the recombinant portion of the aggrecan molecule contains the $\rm E^{1919-1920L}$ bond.
- 46. An assay according to claims 37, 38, 40-45 wherein fragments produced by specific cleavage at the the E^{373} - ^{374}A bond are monitored using a necepitope antibody to the new C-terminus or new N-terminus on fragments generated by cleavage at this bond.
- 47. An assay according to claims 37, 38, 40-45 wherein fragments produced by specific cleavage at the the $E^{1545-1546}G$ bond are monitored using a neoepitope antibody to the new C-terminus or new N-terminus on fragments generated by cleavage at this bond.



- 49. An assay according to claim 37, 38, 40-45 wherein fragments produced by specific cleavage at the the $E^{1819}-^{1820}A$ bond are monitored using a neoepitope antibody to the new C-terminus or new N-terminus on fragments generated by cleavage at this bond.
- 50. An assay according to claim 37, 38, 40-45 wherein fragments produced by specific cleavage at the the $\rm E^{1919-1920}L$ bond are monitored using a neoepitope antibody to the new C-terminus or new N-terminus on fragments generated by cleavage at this bond.
- 51. An assay according to claim 37, 38, 40-45 wherein the ARGSV N-terminus is detected using the monoclonal antibody, BC-3.
- 52. A method for assaying compounds for activity against an ADMP comprising:

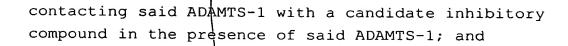
providing an ADMP and an ADMP substrate;

contacting said ADMP with a candidate inhibitory compound in the presence of said ADMP; and

measuring the inhibition of the ADMP activity.

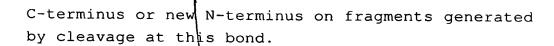
53. A method for assaying compounds for activity against an ADAMTS-1 comprising:

providing an ADAMTS-1 and an ADAMTS-1 substrate;



measuring the inhibition of the ADAMTS-1 activity.

- 54. A method for diagnosing arthritic diseases in a mammal using an antibody according to claim 19 or 20 to detect ADMPs in biological samples.
- 55. An method for detecting ADMP-generated products in biological samples which comprises detecting the new N-terminus or new C-terminus on fragments produced by specific cleavage at an ADMP-sensitive site using a necepitope antibody to the N-terminus or C-terminus on the ADMP-generated fragment.
- 56. An assay according to claim 55 wherein fragments produced by specific cleavage at the the $\mathrm{E}^{373-374}\mathrm{A}$ bond are monitored using a necepitope antibody to the new C-terminus or new N-terminus on fragments generated by cleavage at this bond.
- 57. An assay according to claim 55 wherein fragments produced by specific cleavage at the the E¹⁵⁴⁵-1546G bond are monitored using a neoepitope antibody to the new C-terminus or new N-terminus on fragments generated by cleavage at this bond.
- 58. An assay according to claim 55 wherein fragments produced by specific cleavage at the E¹⁷¹⁴-¹⁷¹⁵G bond are monitored using a necepitope antibody to the new C-terminus or new N-terminus on fragments generated by cleavage at this bond
- 59. An assay according to claim 55 wherein fragments produced by specific cleavage at the $\rm E^{1819-1820}A$ bond are monitored using a necepitope antibody to the new



- 60. An assay according to claim 55 wherein produced by specific cleavage at the $E^{1919-1920}L$ bond is monitored using a neoepitope antibody to the new C-terminus or new N-terminus on fragments generated by cleavage at this bond.
- 61. A method for diagnosing arthritic diseases in a mammal by monitoring specific ADMP-generated aggrecan fragments in biological samples according to any of claims 55-60.
- A method for diagnosing arthritic diseases in a mammal using a nucleic acid probe which hybridizes with a native ADMP nucleic acid sequence according to any of claims 7,8,12,13,17 or 18 to detect ADMP message in biological samples.
- A method for diagnosing a disease in a mammal characterized by an overproduction or an up-regulated production of an ADMP using an antibody to detect ADMPs in biological samples.
- A method for diagnosing a disease in a mammal characterized by an overproduction or an upregulated production of an ADMP by monitoring specific ADMP-generated fragments in biological samples according to any of claims 55-60.
 - A method for diagnosing a disease in a mammal characterized by an overproduction or an upregulated production of an ADMP using a nucleic acid probe which hybridizes with a native ADMP nucleic acid sequence according to any of claims 7,8,12,13,17 or 18 to detect ADMP message in biological samples.

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